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Rev 01/30/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Thomas C. Terwilliger	Docket No.:	S-91,732
Serial No.:	09/512,962	Examiner:	A. Marschel
Filed :	February 25, 2000	Art Unit:	1631

For : LIKELIHOOD-BASED MODIFICATION OF EXPERIMENTAL CRYSTAL STRUCTURE ELECTRON DENSITY MAPS

Mail Stop Appeal Brief - Patents
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

1. Transmitted herewith in triplicate is the Appeal Brief in this application with respect to the Notice of Appeal filed on May 18, 2004.

2. ☐ Applicant claims small entity status.

3. Attached is a Fee Transmittal Form.

Respectfully submitted,

Date: June 02, 2004

Signature of Attorney

Reg. No. 28,351
Phone (505) 665-3112

Ray G. Wilson
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CERTIFICATE OF MAILING/TRANSMISSION (37 CFR 1.8(a))

I hereby certify that this correspondence is, on the date shown below, being:

MAILING

☒ deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Date June 02, 2004

FACSIMILE

☐ transmitted by facsimile to the United States Patent and Trademark Office

Signature

Ray G. Wilson
(type or print name of person certifying)

Rev. 03/05/04

FEE TRANSMITTAL
For FY 2004

Patent fees are subject to annual revision

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT: $330.00

Complete if Known	
Application Number:	09/512,962
Filing Date:	2/25/2000
First Named Inventor:	Thomas C. Terwilliger
Examiner Name:	A. Marschel
Group/Art Unit:	1631
Attorney Docket No.:	S-91,732

METHOD OF PAYMENT (check all that apply)

1. ☒ The commissioner is hereby authorized to charge indicated fees and credit any over payments to:
   Deposit Account Number: **12-2150**
   Deposit Account Name: **Los Alamos National Laboratory**
   ☒ Charge Any Additional Fee Required Under 37 C.F.R. 1.16 and 1.17

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee		Small Entity Fee		Fee Description	Fee Paid
1001	$770	2001	$385	Utility filing fee	
1004	$770	2004	$385	Reissue filing fee	
1005	$160	2005	$80	Provisional filing fee	

SUBTOTAL (1) $000.00

2. EXTRA CLAIM FEES

		Extra Claims	Fee from Fee Paid Below
Total Claims	–20** =	X	=
Independent Claims	–3 ** =	X	=
Multiple Dependent			=

** *or number previously paid, if greater; For Reissues, see below*

Large Entity Fee		Small Entity Fee		Fee Description
1202	$18	2202	$9	Claims in excess of 20
1201	$86	2201	$43	Independent claims in excess of 3
1203	$290	2203	$145	Multiple dependent claim, if not paid.
1204	$86	2204	$43	** Reissue independent claims over original patent
1205	$18	2205	$9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) $

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description	Fee Paid
1051	$130	2051	$65	Surcharge – late filing fee or oath	
1052	$50	2052	$25	Surcharge – late provisional filing fee or cover sheet	
1812	$2,520	1812	$2,520	For filing a request for reexamination	
1251	$110	2251	$55	Extension for reply within first month	
1252	$420	2252	$210	Extension for reply within second month	
1253	$950	2253	$475	Extension for reply within third month	
1254	$1,480	2254	$740	Extension for reply within fourth month	
1255	$2,010	2255	$1,005	Extension for reply within fifth month	
1401	$330	2401	$165	Notice of Appeal	
1402	$330	2402	$165	Filing a brief in support of an appeal	$330.00
1403	$290	2403	$145	Request for oral hearing	
1452	$110	2452	$55	Petition to revive – unavoidable	
1814	$110	2814	$55	Terminal Disclaimer	
1453	$1,330	2453	$665	Petition to revive – unintentional	
1460	$130	1460	$130	Petitions to the Commissioner	
1806	$180	1806	$180	Submission of Information Disclosure Statement	
1809	$770	2809	$385	Filing a submission after final rejection (37 CFR 1.129 (a))	
1810	$770	2810	$385	For each additional invention to be examined (37 CFR 1.129(b))	
1811	$100	1811	$100	Certificate of Correction	
1504	$300	1504	$300	Publication fee for early, voluntary, or normal publication	
1801	$770	2801	$385	Request for Continued Examination (RCE)	

Other fee (specify) _____

SUBTOTAL (3) $

Reduced by Basic Filing Fee Paid

SUBTOTAL FROM 1 $
SUBTOTAL FROM 2 $
SUBTOTAL FROM 3 $330.00

TOTAL AMOUNT OF PAYMENT $330.00

SUBMITTED BY			Complete (if applicable)	
Printed Name:	Ray G. Wilson		Reg. No.	28,351
Signature:	Ray G. Wilson	Date: 06/02/04	Telephone	(505) 665-3112

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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APPEAL BRIEF

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STATEMENT OF THE REAL PARTY IN INTEREST

The Regents of the University of California is the assignee of all right, title, and interest in U.S. Patent Application Serial No. 09/512,962 from the Government of the United States, United States Department of Energy.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences related to this case.

STATUS OF ALL CLAIMS

Claims 10-14 are pending in this case. Claims 10-14 stand rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter.

STATUS OF AMENDMENTS

There are no outstanding amendments in this case.

SUMMARY OF THE INVENTION

An electron density map of an experimental crystal structure is modified by combining experimental phase information with prior knowledge about expected electron density distribution in maps by maximizing a combined likelihood function (Page 5, lines 16-18). A model electron density map is formed (Fig. 1, step 12; Page 17, lines 9-10) from known crystallographic information of an exemplary model crystal structure (Fig. 1, step 10, Page 17, lines 8-9; Page 15, lines 1-14) and model histograms of model electron densities in identified protein and solvent regions of the model electron density map are formed (Fig. 1, steps 14-18; Page 17, lines 10-13). A model probability distribution function is then fitted to the model histograms (Fig. 1, step 18022; Page 17, lines 13-17) to determine factors for a normalization factor, mean value of electron density, and the variance of density distribution over the map (Page 14, lines 12-20; Page 15, lines 15-25). A set of experimental structure factors is then determined from x-ray diffraction data for the experimental crystal structure and an experimental electron density map is formed (Page 16, lines 24-26; Page 17, lines 1-6). Separate experimental histograms of experimental electron densities are formed over protein and solvent regions of the experimental electron density map (Page 16, lines 6-17). Another experimental probability distribution function is fitted to the separate protein and solvent regions of the experimental histograms (Page 15, lines 16-29; Page 16, lines 1-5) to determine an expectation that an experimental electron density value is less than a true value and a variance of experimental map electron density value from a true value (Fig. 2, step 34; Page 16, lines 6-19). The overall experimental log-likelihood of the electron density in the protein and solvent regions of the experimental map is then determined from the experimental probability distribution function (Page 9, Eqn. (6); Page 19, lines 1-6). It is determined how the experimental log-likelihood of the electron density of the protein and solvent regions of the structure factor experimental electron density map would change as each experimental changes to output a revised log-likelihood of any value of each experimental structure factor (Fig. 2, steps 36-42; Page 19, lines 8-14; Page 9, lines 1-4; Page 10, lines 1-16) and a new set of structure factors is formed from the revised log-likelihood of experimental structure factor values.

Finally, a revised experimental electron density map is formed from the revised structure factors (Page 19, lines 20-22).

ISSUE PRESENTED FOR REVIEW

Do the methods recited in Claims 10-14 recite statutory subject matter under 35 U.S.C. §101 and entitled to a patent?

GROUPING OF THE CLAIMS

Applicants do not believe that any special grouping of the claims leads to a better understanding of the issues.

ARGUMENT

Appellant respectfully traverses the rejection of the claims under 35 U.S.C. §101 as directed to non-statutory subject matter. The Examiner has rejected Claims 10-14 under 35 U.S.C. §101, remarking that the claimed process is directed to non-statutory subject matter since "no physical transformation is controlled by the claim algorithm," which "only manipulates an electron density map which is reasonably data and not a physical material." As noted in MPEP 2106.IV.B.2.(b).(i), a process is clearly statutory "if it requires physical acts to be performed outside the computer . . . . But, "[i]f a claim does not clearly fall into one or both of the safe harbors, the claim may still be statutory if it is limited to a practical application in the technological arts."

> The notion of "physical transformation" can be misunderstood. In the first place, it is not an invariable requirement, but merely one example of how a mathematical algorithm may bring about a useful application.
> ***AT&T Corp. v. Excel Communications, Inc.***, 172 F.3d 1352, 50 USPQ 2d 1447, 1454 (Fed. Cir. 1999), *cert denied*, 120 S. Ct. 368 (1999), *on remand*, 52 USPQ2d 1865 (D. Del. 1999)
>
> Today, we hold that the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm,

> formula, or calculation, because it produces "a useful, concrete and tangible result"--a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades.
> ***State Street Bank & Trust Co. v. Signature Fin. Group, Inc.***, 47 USPQ 2d 1596, 1601 (Fed. Cir.), ***cert. denied***, 525 U.S. 1093 (1999)
>
> It is clear from the written description of the . . . patent that AT&T is only claiming a process that uses the Boolean principle in order to determine the value of the PIC indicator. The PIC indicator represents information about the call recipient's PIC, a useful, non-abstract result that facilitates differential billing of long-distance calls made by an IXC's subscriber. Because the claimed process applies the Boolean principle to produce a use, concrete, tangible result without pre-empting other uses of the mathematical principle on its face the claims process comfortably falls within the scope of Section 101. *See Arrhythimia Research Tech. Inc. v. Corazonix Corp.*, 958 R.2d 1053, 1060, 22 USPQ2d 1033, 1039 (Fed. Cir. 1992) ('That the product is numerical is not a criterion of whether the claim is directed to statutory subject.') *Id.*.
> ***AT&T Corp. v. Excel Communications, Inc.***, *supra.* at 1452.

Appellant's claimed method is the application of mathematical algorithms to modify "an electron density map of an experimental crystal structure," resulting in a new electron density map, as recited in Claim 10. There is no longer in the law any requirement that the method result in any "physical transformation" as would be required by the Examiner. Further, the application of the recited mathematical manipulations is clearly directed to a specified application, the formation of a revised electron density map of a crystal structure from a starting electron density map. There is no attempt to claim or forestall the use of any mathematical manipulation in any other application. See, e.g., the following claim steps:

(a) forming a model electron density map from known crystallographic information of an exemplary model crystal structure;

(b) forming model histograms of model electron densities in identified protein and solvent regions of the model electron density map;

(c) fitting a model probability distribution function . . .to the model histograms . . .;

(d) determining a set of experimental structure factors from x-ray diffraction data for the experimental crystal structure and forming an experimental electron density map;

(g) forming from the revised log-likelihood of experimental structure factor values a new set of structure factors;

(j) forming a revised experimental electron density map from the revised structure factors.

Independent Claim 10 and dependent Claims 11-14 clearly produce a concrete, tangible result within the teachings of AT&T Corp., *supra.,* and State Street Bank & Trust Co., supra. Even assuming that the electron density map is "reasonably data and not a physical material," as characterized by the Examiner, this is not a criteria for determining whether the claims are directed to statutory subject matter.

CONCLUSION

Claims 10-14 recite a method that is a "practical application in the technological arts" producing a useful result and constitute statutory subject matter under 35 U.S.C. §101. The rejection of Claims 10-14 as being directed to nonstatutory subject matter should be withdrawn.

Respectfully submitted,

Date: June 1, 2004

Signature of Attorney

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APPENDIX A - CLAIMS ON APPEAL

10. A method for improving an electron density map of an experimental crystal structure, comprising the steps of:

(a) forming a model electron density map from known crystallographic information of an exemplary model crystal structure;

(b) forming model histograms of model electron densities in identified protein and solvent regions of the model electron density map;

(c) fitting a model probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - c_k)^2}{2\sigma_k^2}\right\}$$

to the model histograms, where k is separately indexed over the protein and solvent regions of the model map, $p(\rho_T)$ is a probability of an electron density at a point, w_k is a normalization factor, ρ is electron density, c_k is a mean value of ρ, and σ_k is a variance of ρ, where the fitting determines the coefficients w_k, c_k, and σ_k;

(d) determining a set of experimental structure factors from x-ray diffraction data for the experimental crystal structure and forming an experimental electron density map;

(e) forming separate experimental histograms of experimental electron densities over protein and solvent regions of the model electron density map;

(f) fitting an experimental probability distribution function defined by

$$p(\rho_T) = \sum_k w_k \exp\left\{-\frac{(\rho - \beta c_k)^2}{2\left(\beta\sigma_k^2 + \sigma_{map}^2\right)}\right\}$$

to separate protein and solvent regions of the experimental histograms, where β is an expectation that an experimental value of ρ is less than a true value and σ_{map} is a variance, where the fitting determines the coefficients β and σ_{map};

(g) determine the overall experimental log-likelihood of the electron density in the protein and solvent regions of the experimental map from the experimental probability distribution function

$$LL\left(\rho\left(\mathbf{x},\{\mathbf{F_h}\}\right)\right) = \ln\left[p\left(\rho(\mathbf{x})|PROT\right)p_{PROT}(\mathbf{x}) + p\left(\rho(\mathbf{x})|SOLV\right)p_{SOLV}(\mathbf{x})\right]$$

where $p_{PROT}(\mathbf{x})$ is the probability that **x** is in the protein region and $p\left(\rho(\mathbf{x})|PROT\right)$ is the conditional probability for $\rho(\mathbf{x})$ given that $\mathbf{x}$ is in the protein region, and $p_{SOLV}(\mathbf{x})$ and $p\left(\rho(\mathbf{x})|SOLV\right)$ are the corresponding quantities for the solvent region;

(h) determine how the experimental log-likelihood of the electron density of the protein and solvent regions of the structure factor experimental electron density map would change as each experimental structure factor changes to output a revised log-likelihood of any value of each experimental structure factor;

(i) forming from the revised log-likelihood of experimental structure factor values a new set of structure factors; and

(j) forming a revised experimental electron density map from the revised structure factors.

11. The method according to Claim 10, wherein step (a) further includes a step of selecting the model crystal structure to be similar in size, data resolution, and atomic displacement factors to the experimental crystal structure.

12. The method according to Claim 10, wherein step (b) further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points as "solvent."

13. The method according to Claim 11, wherein step (b) further includes a step of identifying protein and solvent regions by designating all points within a selected distance of an atom as "protein" and all other points as "solvent."

14. The method according to Claim 10, wherein step (h) includes steps of forming a Taylor's series expansion of the log-likelihood of the experimental electron density map and evaluating terms of the Taylor's series expansion using a Fast Fourier Transform.